Office of Environmental Health Hazard Assessment

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Winston H. Hickox
Agency Secretary

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Dr. Scott Masten
Office of Chemical Nomination and Selection
NIEHS/NTP
P.O. Box 12233
Research Triangle Park, North Carolina 27709

Rec'd 10/9/01

Dear Dr. Masten:

This is written in response to the request for comment on the recommendations for testing by the National Toxicology Program (NTP) Interagency Committee for Chemical Evaluation and Coordination (ICCEC) published in the July 25, 2001 Federal Register [66(143): 38717-38719]. In particular, we are commenting on the ICCEC recommendations to test the polybrominated diphenyl ethers (PBDEs) and are recommending additional testing of the PBDEs.

PBDEs are widely used in the United States as flame retardant additives to foams, plastics and textiles. The ICCEC recommended that three specific congeners of PBDEs (those most prevalent in most human tissue samples) be tested for subchronic toxicity, developmental neurotoxicity and chronic toxicity. As outlined below, we recommend that the testing of these chemicals include standard two-year carcinogenicity bioassays, and developmental neurotoxicity and thyroid disruption studies that employ additional groups treated at very low doses, in normal and iodine-deficient animals.

1. Carcinogenicity testing should be conducted on 2,2',4,4'-tetraBDE; 2,2',4,4',5-pentaBDE and 2,2',4,4',5,5'-hexaBDE. The ICCEC recommended that these specific PBDE congeners be tested in chronic studies. However, according to the Federal Register notice, the ICCEC did not recommend carcinogenicity testing. We strongly recommend that carcinogenicity testing of these same PBDEs also be undertaken.

DDT and PCBs, compounds structurally similar to the PBDEs, are carcinogenic in animals and there is some direct evidence that PCBs are carcinogenic in humans. DDT, PCBs and PBDEs appear to function through many of the same receptors (Hooper and McDonald, 2000; McDonald, 2001); thus, it is critical to determine if the PBDEs accumulating in human tissues pose a cancer risk.

As noted in our earlier letter of December 8, 1999, only the fully brominated deca-PBDE has been tested for carcinogenicity, yielding equivocal findings (NTP, 1986). The deca-PBDE congener is not readily absorbed (0.3 %), is rapidly eliminated, and has very low potential for

enzyme induction and thyroid hormone disruption (Zhou et al., 2001). The tetra- and penta-PBDEs, on the other hand, are completely absorbed, more slowly eliminated, and much more potent in inducing liver enzymes and disrupting thyroid hormone balance (Zhou et al., 2001; Hooper and McDonald, 2000). The hexa-PBDEs would also be predicted to be effective in inducing liver enzymes and disrupting thyroid hormone function. In addition, 2, 2',4,4'-tetra-BDE has been shown to bind covalently to macromolecules following *in vivo* administration (Örn and Klassen-Weller, 1998). 2,2',4,4'-TetraBDE, 2,2',4,4',5-penta-BDE, and 2,2',4,4',5,5'-hexaBDE are therefore likely to have greater carcinogenic potential than the deca-PBDE tested previously by NTP, and they should be tested in standard two-year rodent bioassays.

2. Additional iodine-deficient and low-dose exposure groups should be included in NTP's developmental neurotoxicity studies of 2,2',4,4'-tetraBDE; 2,2',4,4',5-pentaBDE and 2,2',4,4',5,5'-hexaBDE. The potential for these compounds to disrupt thyroid hormone function should also be assessed in these additional iodine-deficient and low-dose exposure groups.

Given the similarities noted above between PBDEs and PCBs, two of the most important toxicological endpoints of concern for low, environmental exposures to the PBDEs are likely to be neurodevelopmental deficits and thyroid hormone disruption (McDonald, 2001). Thyroid hormone disruption and the related condition of iodine deficiency during pregnancy are well-established mechanisms of causing neurodevelopmental deficits in progeny of humans and rodents (Morreale de Escobar et al., 2000). A troubling fact is that about 15 percent of women of child-bearing age in the U.S. are iodine deficient (Hollowell et al., 1998). Iodine-deficient individuals are likely to be at greater risk of experiencing adverse health effects following exposure to thyroid hormone disrupting chemicals than are individuals with sufficient iodine intake. To better address the risks to sensitive populations, we recommend that additional groups of iodine-deficient rodents be included in the testing protocol. In addition, given that low-dose, non-linear responses have been observed with other endocrine-disrupting agents (NTP, 2001), we recommend that the range of doses at which these PBDE congeners are tested in normal and iodine-deficient animals be expanded at the lower end by including at least two additional treatment levels at very low doses.

Please feel free to contact me at (510) 622-3192 or Dr. Thomas A. McDonald at (510) 622-3187 regarding these comments.

Sincerely,

Martha S. Sandy, M.P.H., Ph.D., Chief
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